REMARKS

The present invention relates to compositions containing a drug coated with a protein, and methods for treating hyperplasia using these compositions.

By the present communication, the specification has been amended to clarify the claim of priority. The present application is a continuation-in-part of U.S. Patent Application Serial No. 09/446,783, filed 16 May 2000, which is a 371 of PCT/US98/13272, which in turn, is a continuation-in-part of 2 prior applications—Provisional Application No. 60/051,021, and Utility Application No. 08/926,155.

In addition, by the present communication, claims 1, 9, 17, 18, 25, 29 and 30, have been amended to define Applicants' invention with greater particularity. No new matter has been introduced by the subject amendments as the amended claim language is fully supported by the specification and original claims. As a result of these amendments, claims 2 and 19 have been cancelled without prejudice. Accordingly, claims 1, 3-18 and 20-30 remain pending in this application. The present status of all claims in the application is provided in the listing of claims presented herein beginning on page 3 of this communication.

Priority

The Examiner's assertion that Applicants' claim of priority back to 2/22/93 is improper is respectfully traversed. However, to reduce the issues and expedite prosecution, the claim of priority has been streamlined by the present communication.

As acknowledged by the Examiner, international application PCT/US98/13272 properly claims priority to both Provisional Application No. 60/051,021 (filed 6/27/97), and Utility Application No. 08/926,155 (filed 9/9/97). Accordingly, it is respectfully submitted that Applicants are entitled to the claim of priority back to 6/27/97 (the priority date of '021), and not 9/9/97 as incorrectly asserted in the Office Action at page 3, line 5.

Rejection under 35 U.S.C. §112, first paragraph

The rejection of claims 1-16, 18-20 and 23-28 under 35 U.S.C. §112, first paragraph, is respectfully traversed.

Applicants respectfully disagree with the Examiner's assertion that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." (See page 3, lines 18-20 of the Office Action). This conclusion is based on an erroneous evaluation of the Wands factors by the Examiner, as follows.

1) The nature of the invention (see page 4 of the Office Action)

Contrary to the Examiner's characterization of the invention as encompassing "administering **any** drug with a protein to treat hyperplasia" (see page 4, line 10 of the Office Action; emphasis in original), the claims, as amended, require use of a drug selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof (in combination with a protein) for the treatment of hyperplasia.

2) The breadth of the claims (see page 4 of the Office Action)

Applicants respectfully disagree with the Examiner's reference to the alleged "complex nature of the claims..." (See page 4, line 11 of the Office Action). Contrary to the Examiner's assertion, the claims are drawn specifically to methods of treating a specific indication (i.e., hyperplasia) employing a defined group of compounds (i.e., a drug selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof), wherein the drug is coated with a protein.

3) Guidance of the specification (see page 4 of the Office Action)

The guidance provided by the present specification is respectfully submitted to be commensurate in scope with the claims, as amended.

4) Working examples (see pages 4-5 of the Office Action)

There is no requirement that Applicants present any working examples to support the claimed invention. Indeed, even if there were no examples included in the specification, the present invention is submitted to be fully enabled by the present disclosure. The compounds appropriate to use are fully disclosed (i.e., a drug selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof, wherein the drug is coated with a protein), as is the protocol for administration of such compounds.

Moreover, the specification provides examples of administration of a prototypical pharmaceutically active agent contemplated for use in the practice of the present invention for the precise purpose to which the present claims are directed (see examples at pages 14-35 of Applicants' specification). Nothing more is required.

5) Predictability of the art (see page 5 of the Office Action)

Applicants respectfully disagree with the Examiner's reference to an alleged "lack of significant guidance from the specification or the prior art..." (see page 5, lines 3-4 of the Office Action). Contrary to the Examiner's assertion, the specification is submitted to provide ample support for the claimed subject matter, e.g., methods for treating hyperplasia in a subject in need thereof, said methods comprising administering to said subject an effective amount of a composition comprising an amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

6) The amount of experimentation necessary (see page 5 of the Office Action)

In this section of the Office Action, the Examiner has provided no support for the assertion that "an artisan of ordinary skill would undergo undue experimentation in deducing which drugs actually treat hyperplasia within applicant's scope." (See page 5, lines 7-9 of the Office Action). Contrary to the Examiner's assertion, no experimentation is required to determine the compounds that would be capable of treating hyperplasia according to the

invention. Attention is directed to the language of claim 1, which requires "a drug selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof." What experimentation is required for one of skill in the art to identify a compound as a member of any of these well defined classes of compounds? None.

7) The state of the art (see page 5 of the Office Action)

As acknowledged by the Examiner, the state of the prior art recognizes various agents as having utility for the treatment of hyperplasia. Applicants do not assert to have discovered any new agents for the treatment of hyperplasia—instead, Applicants have developed new formulations containing such agents, and new methods of treatment employing such formulations.

In addition to the Wands factors discussed above, the Examiner has failed to further consider the additional Wands factor of **the relative skill of those in the art** which in the field of the present invention is high. In view of this acknowledged high level of skill, it is respectfully submitted that the present disclosure provides more than adequate enablement of the claimed methods and formulations. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection of claims 1-16, 18-20 and 23-28 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 18-20 and 23-28 under 35 U.S.C. §102(b) over Mathiowitz

The rejection of claims 18-20 and 23-28 under 35 U.S.C. §102(b), as allegedly being anticipated by Mathiowitz et al. (U.S. Patent No. 5,271,961), is respectfully traversed. Applicants' invention, as defined, for example, by claim 18, distinguishes over Mathiowitz by requiring compositions for treatment of hyperplasia, said compositions comprising (i) at least one amorphous drug in nanoparticle form, and (ii) protein, wherein the drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Mathiowitz does not disclose such compositions. Instead, Mathiowitz contemplates microspheres containing insulin. Clearly, the Mathiowitz formulations are different from the formulations contemplated by the present claims.

Applicants' invention, as defined, for example, by claim 25, further distinguishes over Mathiowitz by requiring compositions for reducing neointimal hyperplasia associated with vascular interventional procedure(s), said compositions comprising at least one amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Mathiowitz does not disclose such compositions. Instead, Mathiowitz contemplates microspheres containing insulin. Clearly, the Mathiowitz formulations are different from the formulations contemplated by the present claims.

Applicants' invention, as defined, for example, by claim 29, still further distinguishes over Mathiowitz by requiring methods to reduce the toxicity of a drug that inhibits proliferation and migration of cells, said methods comprising combining said drug, in amorphous form and in the form of nanoparticles, with a biocompatible protein, wherein said drug is coated with said protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Mathiowitz does not disclose such methods.

Applicants' invention, as defined, for example, by claim 30, still further distinguishes over Mathiowitz by requiring pharmaceutical formulations with reduced toxicity, said formulations comprising an amorphous drug in nanoparticle form, wherein said drug inhibits proliferation and cell migration, wherein said drug is coated with a biocompatible protein, and wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Mathiowitz does not disclose such formulations.

Rejection of Claims 18-21 and 23-30 under 35 U.S.C. §102(b) over Grinstaff

The rejection of claims 18-21 and 23-30 under 35 U.S.C. §102(b), as allegedly being anticipated by Grinstaff et al. (U.S. Patent No. 5,498,421), is respectfully traversed. Applicants' invention, as defined, for example, by claim 18, distinguishes over Grinstaff by requiring compositions for treatment of hyperplasia, said compositions comprising (i) at least one amorphous drug in nanoparticle form, and (ii) protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Grinstaff does not disclose such compositions.

Applicants' invention, as defined, for example, by claim 25, further distinguishes over Grinstaff by requiring compositions for reducing neointimal hyperplasia associated with vascular interventional procedure(s), said compositions comprising at least one amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Grinstaff does not disclose such compositions.

Applicants' invention, as defined, for example, by claim 29, still further distinguishes over Grinstaff by requiring methods to reduce the toxicity of a drug that inhibits proliferation and migration of cells, said methods comprising combining said drug, in amorphous form and in the form of nanoparticles, with a biocompatible protein, wherein said drug is coated with said protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Grinstaff does not disclose such methods.

Applicants' invention, as defined, for example, by claim 30, still further distinguishes over Grinstaff by requiring pharmaceutical formulations with reduced toxicity, said formulations comprising an amorphous drug in nanoparticle form, wherein said drug inhibits proliferation and cell migration, wherein said drug is coated with a biocompatible protein, and wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Grinstaff does not disclose such formulations.

Rejection of Claims 1-4, 6-13, 15, 17-21 and 23-30 under 35 U.S.C. §102(b) over Kunz

The rejection of claims 1-4, 6-13, 15, 17-21 and 23-30 under 35 U.S.C. §102(b), as allegedly being anticipated by Kunz et al. (U.S. Patent No. 5,733,925), is respectfully traversed. Applicants' invention, as defined, for example, by claim 1, distinguishes over Kunz by requiring methods for treating hyperplasia in a subject in need thereof, said methods comprising administering to said subject an effective amount of a composition comprising an amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Kunz does not disclose such methods. Instead, Kunz contemplates use of drug conjugated with a binding protein. Thus, Kunz requires a chemical modification of drug by conjugation thereto with a binding protein, rather than the much simpler physical process of coating drug with protein, as contemplated by the present claims.

Applicants' invention, as defined, for example, by claim 9, further distinguishes over Kunz by requiring methods for reducing neointimal hyperplasia associated with vascular interventional procedure(s) in a subject in need thereof, said methods comprising administering

to said subject an effective amount of a composition comprising at least one amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Kunz does not disclose such methods. Instead, Kunz contemplates use of drug conjugated with a binding protein. Thus, Kunz requires a chemical modification of drug by conjugation thereto with a binding protein, rather than the much simpler physical process of coating drug with protein, as contemplated by the present claims.

Applicants' invention, as defined, for example, by claim 17, still further distinguishes over Kunz by requiring methods to reduce proliferation and cell migration in a subject undergoing a vascular interventional procedure, said methods comprising systemically administering to said subject before, during or after said procedure, a formulation comprising (i) an amorphous drug in nanoparticle form, wherein said drug inhibits proliferation and cell migration, and (ii) a biocompatible protein wherein said drug is coated with said protein, and wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Kunz does not disclose such methods. Instead, Kunz contemplates use of drug conjugated with a binding protein. Thus, Kunz requires a chemical modification of drug by conjugation thereto with a binding protein, rather than the much simpler physical process of coating drug with protein, as contemplated by the present claims.

Applicants' invention, as defined, for example, by claim 25, further distinguishes over Kunz by requiring compositions for reducing neointimal hyperplasia associated with vascular interventional procedure(s), said compositions comprising at least one amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Kunz does not disclose such compositions. Instead, Kunz requires a chemical modification of drug by conjugation thereto with a binding protein, rather than the much simpler physical process of coating drug with protein, as contemplated by the present claims.

Applicants' invention, as defined, for example, by claim 29, still further distinguishes over Kunz by requiring methods to reduce the toxicity of a drug that inhibits proliferation and migration of cells, said methods comprising combining said drug, in amorphous form and in the form of nanoparticles, with a biocompatible protein, wherein said drug is coated with said protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Kunz does not disclose such methods.

Applicants' invention, as defined, for example, by claim 30, still further distinguishes over Kunz by requiring pharmaceutical formulations with reduced toxicity, said formulations comprising an amorphous drug in nanoparticle form, wherein said drug inhibits proliferation and cell migration, wherein said drug is coated with a biocompatible protein, and wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Kunz does not disclose such formulations.

Rejection of Claims 5, 14, 16 and 22 under 35 U.S.C. §103(a) over Kunz

The rejection of claims 5, 14, 16 and 22 under 35 U.S.C. §103(a), as allegedly being obvious over Kunz is respectfully traversed.

Applicants' invention, as defined, for example, by claim 5, distinguishes over Kunz by requiring methods for treating hyperplasia in a subject in need thereof, said method comprising administering to said subject an effective amount of a composition comprising an amorphous

drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof, wherein the effective amount falls in the range of about 0.01 mg/kg up to about 15 mg/kg for a human subject, and wherein said administration of said composition is repeated over a dosing cycle between 1 day and 6 months.

Kunz does not disclose or suggest such methods. Instead, Kunz contemplates methods which use drug conjugated with a binding protein. Thus, Kunz requires a chemical modification of drug by conjugation thereto with a binding protein, rather than the much simpler physical process of coating drug with protein, as contemplated by the present claims.

Applicants' invention, as defined, for example, by claim 14, further distinguishes over Kunz by requiring methods for reducing neointimal hyperplasia associated with vascular interventional procedure(s) in a subject in need thereof, said method comprising administering to said subject an effective amount of a composition comprising at least one amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof, wherein said effective amount falls in the range of about 0.01 mg/kg up to about 15 mg/kg for a human subject, and wherein said administration of said composition is repeated over a dosing cycle between 1 day and 6 months.

Kunz does not disclose or suggest such methods.

Applicants' invention, as defined, for example, by claim 16, still further distinguishes over Kunz by requiring methods for reducing neointimal hyperplasia associated with vascular interventional procedure(s) in a subject in need thereof, said methods comprising administering to said subject an effective amount of a composition comprising at least one amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or

more thereof, wherein said composition is administered by deployment of a stent containing said at least one drug coated thereon.

Kunz does not disclose or suggest such methods.

Applicants' invention, as defined, for example, by claim 22, still further distinguishes over Kunz by requiring compositions for treatment of hyperplasia, said compositions comprising (i) amorphous paclitaxel in nanoparticle form, and (ii) protein.

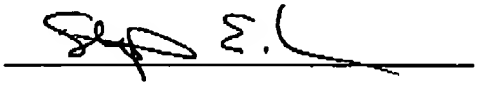
Kunz does not disclose or suggest such compositions.

Conclusion

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: September 14, 2004

By: 

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